Complete Summary

GUIDELINE TITLE

Preoperative or postoperative therapy for the management of patients with stage II or III rectal cancer: guideline recommendations.

BIBLIOGRAPHIC SOURCE(S)

Wong R, Berry S, Spithoff K, Simunovic M, Chan K, Agboola O, Dingle B, Rumble RB, Cummings B, Gastrointestinal Cancer Disease Site Group. Preoperative or postoperative therapy for the management of patients with stage II or III rectal cancer: guideline recommendation. Toronto (ON): Cancer Care Ontario (CCO); 2008 Jul 15. 77 p. (Evidence-based series; no. 2-4). [72 references]

GUIDELINE STATUS

This is the current release of the guideline.

The EVIDENCE-BASED SERIES report, initially the full original Guideline or Evidence Summary, over time will expand to contain new information emerging from their reviewing and updating activities.

Please visit the Cancer Care Ontario Web site for details on any new evidence that has emerged and implications to the guidelines.

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SCOPE

DISEASE/CONDITION(S)

Stage II and II rectal cancer

GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness
Management
Treatment

CLINICAL SPECIALTY

Gastroenterology
Internal Medicine
Oncology
Radiation Oncology
Surgery

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

- To evaluate if patients with resectable clinical stage II or III rectal cancer, following appropriate preoperative staging tests, should be offered preoperative radiotherapy (RT) (with or without chemotherapy [CT])
- To evaluate the role of postoperative RT and/or CT for patients with resected stage II or III rectal cancer who have not received preoperative RT, in terms of improving survival and delaying local recurrence

TARGET POPULATION

Adult patients with clinically resectable or resected stage II or III rectal cancer

INTERVENTIONS AND PRACTICES CONSIDERED

1. Preoperative radiotherapy (RT) (with or without chemotherapy [CT])
2. Postoperative RT and/or CT

MAJOR OUTCOMES CONSIDERED

- Overall survival
- Cause-specific survival
- Recurrence-free survival
- Local control
- R0 resection
- Sphincter preserving surgery
- Quality of life
- Acute toxicities
- Postoperative morbidity (within 30 days of surgery)
- Late toxicities (> 90 days after surgery)

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Preoperative Therapy

For the comparison of preoperative radiotherapy (RT) with surgery alone or other preoperative or postoperative approaches, literature search results for 1966 to December 2006 were adopted from the published Cochrane review by Wong et al. The literature review was updated by searching entries to MEDLINE (December 2006 to May week 4 2007), EMBASE (to week 21, 2007), the Cochrane Library (Issue 2, 2007), and the proceedings of the 2007 American Society of Clinical Oncology (ASCO) meetings for relevant trial reports.

For the comparison of preoperative chemoradiotherapy (CRT) with surgery or another preoperative or postoperative approach, the literature search strategy described in the Cochrane review was used and article selection was performed specifically to identify articles with preoperative CRT as one of the trial arms.

Relevant articles and abstracts were selected and reviewed, and the reference lists from these sources were searched for additional trials. A search of personal reprint files was also conducted.

Study Selection Criteria

Articles were selected for inclusion in this systematic review of the evidence if they met the following criteria:

1. The article reported on randomized controlled trials (RCTs) or systematic reviews of RCTs.
2. The RCT results were reported on patients with clinical stage II or III resectable rectal cancer, although the RCT could have included earlier stage patients. The original intention was to include only studies that involved earlier stage patients if they were stratified by stage. However, there were no studies that incorporated this stratification, so this criterion was modified to include studies where results were reported by stage.
3. The RCTs compared preoperative RT (with or without CT) to surgery alone or an alternative preoperative or postoperative therapy (e.g., preoperative CRT vs. preoperative RT).
4. The article reported on relevant outcomes (see "Major Outcomes Considered" above)
5. The surgery received by the RCT patients was potentially curative. Total mesorectal excision (TME) was not mandatory.
6. The RCT or systematic review was reported as a fully published report or published abstract.

7. The RCT or systematic review was reported in English, as translation resources were not available.

Postoperative Therapy

Searches were conducted for the years from 1988 to September (week 2) 2007 on MEDLINE, 1996 through to week 38, 2007 on EMBASE, October 2002 on CANCERLIT, and through to Issue 3, 2007 of the Cochrane Library, using the MeSH terms "rectal neoplasm", "colorectal neoplasm", "drug therapy", "adjuvant chemotherapy", "adjuvant radiotherapy", "combined modality therapy", and the text word "adjuvant". These search terms were combined with search words for the following publication types: randomized controlled trials, meta-analyses, and systematic overviews. Personal reprint files were also searched and citations from retrieved articles were reviewed. Abstracts published in the proceedings of the 1999 through 2007 annual meeting of the American Society of Clinical Oncology (ASCO) and the 1999 through 2006 annual meeting of the American Society for Therapeutic Radiation and Oncology (ASTRO) were also searched for relevant information. The National Cancer Institute (NCI) database (http://www.cancer.gov/search/clinical_trials/) was searched for relevant ongoing clinical trials on December 10, 2007.

Inclusion Criteria

Articles were selected for inclusion in this systematic review of the evidence if they met the following criteria:

1. The RCTs enrolled patients with stage II or III rectal carcinoma who had undergone resection with curative intent. Information on tumour staging is found in Appendix 1 in the original guideline document. While many of the available studies reported on patients with colorectal cancer, this review considered only studies that presented data for patients with stage II or III rectal carcinoma separately from colon cancer patients.
2. Syntheses of evidence were in the form of systematic overviews and meta-analyses of RCTs.
3. Studies were published in the English language, as translation resources were not available.

NUMBER OF SOURCE DOCUMENTS

Preoperative Therapy

Eight systematic reviews and six trials were included in the review.

Postoperative Therapy

Twenty-nine randomized controlled trials (RCTs), one systematic review, and six meta-analyses were identified.

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Expert Consensus (Committee)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

METHODS USED TO ANALYZE THE EVIDENCE

Meta-Analysis of Randomized Controlled Trials
Review of Published Meta-Analyses
Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Preoperative Therapy

A meta-analysis of clinically homogeneous trial results and a sensitivity analysis for quality of total mesorectal excision (TME) and radiotherapy (RT) dose (higher versus lower) were planned. However, due to the limited number of randomized controlled trials (RCTs) reporting data for stage II and III rectal cancer in each comparison, the potential bias associated with a pooled estimate for this small subset of trials, and heterogeneity between trials, no meta-analyses were performed.

Postoperative Therapy

Where possible, the data were pooled to estimate the overall effect on both survival and local control for the following comparisons: RT versus observation alone, chemotherapy (CT) versus observation alone (systemic and oral), combined chemo-radiotherapy (CRT) versus observation, CT versus RT, CT versus CT, CRT versus RT alone, CRT versus CT alone, and CRT versus CRT. The results for patients with stage II and III rectal cancer were combined in meta-analyses for this report in the manner in which data were presented in the published reports. It was not possible to separate results of stage II versus those with stage III disease. Individual patient data were not available for these analyses. When survival and disease-free survival were not reported, they were estimated from published graphs (estimated data). Where available, data for five-year survival and disease-free survival were abstracted and reported. Data on local recurrence reported at the time of follow-up in each study were pooled even though follow-up times were different across studies. Combining data in this way assumes a constant hazard ratio of risks between the groups being compared.

The study results were pooled using Review Manager 4.2.7 (RevMan Analyses 1.0.2; version date: November 2003; © 2003 the Cochrane Collaboration), which is freely available through the Cochrane Collaboration. Results are expressed as relative risk ratios (RR), where RR <1.0 indicates lower risk of an event in the experimental treatment group, RR >1.0 indicates lower risk in the control group, and RR=1 indicates no difference in risk between the groups.

The numbers need to treat (or harm) (NNT) for study results were calculated from the RRs with the Visual Rx NNT calculator freely available online (http://www.nntonline.net/), using the methodology described by Cates.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

Development and Internal Review

This evidence-based series (EBS) was developed by the gastrointestinal (GI) Disease Site Group (DSG) of the Cancer Care Ontario's Program in Evidence-Based Care (CCO PEBC). The series is a convenient and up-to-date source of the best available evidence on preoperative or postoperative therapy for stage II or III rectal cancer, developed through review of the evidentiary base, evidence synthesis, and input from external review participants in Ontario. The GI DSG is comprised of medical oncologists, radiation oncologists, surgeons, and a community representative. A complete list of GI DSG members can be found on the CCO website at http://www.cancercare.on.ca/english/toolbox/qualityguidelines/diseasesite/gastro-ebs/gastro-dsg/.

Discussions by the members of the Gastrointestinal Disease Site Group (GI DSG) concerning the draft recommendations involved the following:

1. Current data suggest that chemoradiotherapy (CRT) should be part of the adjuvant treatment of stage II and III rectal cancer as it does improve both local recurrence and survival.
2. A major debate developed about whether radiotherapy (RT) should be administered before or after surgery. Preoperative short-course RT seems better where local control and toxicity are concerned compared to a standard five-week course of postoperative RT. However, using preoperative RT may lead to the treatment of some patients who do not need it and may interfere with the selection for chemotherapy if disease stage is altered, although recent evidence demonstrates that stage is not altered when short-course RT is followed by surgery within 10 days.
3. The role of chemotherapy (CT) alone or combined with RT needs to be clarified. Two areas of concern are the need for adjuvant CT for stage II patients and the duration of CT for stage III patients. The members of the GI DSG felt it was crucial to support clinical trials addressing these issues.
4. Some members felt that local recurrence rates after surgery in the reviewed trials were much higher than rates expected by current standards that include total mesorectal excision (TME).
5. The survival advantage of adjuvant treatments for rectal cancer is small and the side effects significant; further improvements in effective therapy are needed.
6. There was unanimous agreement that patients should be informed of the emerging data from ongoing adjuvant therapy trials and that they should be encouraged to participate in clinical trials.

7. There was considerable debate and discussion about the contents of the qualifying statement indicating that oxaliplatin and capecitabine should be considered. While there was general agreement, some members disagreed with including treatments not supported by direct evidence.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Report Approval Panel

Prior to the submission of this evidence-based series (EBS) draft report for external review, the report was reviewed and approved by the Program in Evidence-based Care (PEBC) Report Approval Panel, which consists of two members, including an oncologist, with expertise in clinical and methodology issues.

External Review by Ontario Clinicians

Following the review and discussion of Section 1: Recommendations and Section 2: Evidentiary Base (of the original guideline document) and review and approval of the report by the PEBC Report Approval Panel, the Gastrointestinal Cancer Disease Site Group (GI DSG) circulated Sections 1 and 2 to external review participants in Ontario for review and feedback.

Methods

Feedback was obtained through a mailed survey of 129 external review participants in Ontario (27 medical oncologists, 19 radiation oncologists, and 84 surgeons). The survey consisted of items evaluating the methods, results, and interpretive summary used to inform the draft recommendations and whether the draft recommendations should be approved as a guideline. Written comments were invited. The survey was mailed out on April 28, 2008. Follow-up reminders were sent at two weeks (post card) and four weeks (complete package mailed again). The GI DSG reviewed the results of the survey.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Preoperative Therapy

- Preoperative chemoradiotherapy (CRT) is preferred, compared to preoperative radiotherapy (RT) (standard fractionation: longer course: 45-50.4 gray (Gy) in 25-28 fractions) alone, to decrease local recurrence.
- Preoperative CRT is preferred, compared with a postoperative approach, to decrease local recurrence and adverse effects.
- For patients with relative contraindications to chemotherapy (CT) in the preoperative period, acceptable alternatives are preoperative standard fractionation (longer course; 45-50.4Gy in 25-28 fractions) or hypofractionation (short course; 25Gy in 5 fractions) RT alone followed by surgery guided by the risk of adverse effects.
- Patients eligible for preoperative RT+/-CT should also be considered for adjuvant CT.

Postoperative Therapy

- Patients with resected stage II or III rectal cancer who have not received preoperative RT should be offered postoperative therapy with concurrent CRT in addition to fluoropyrimidine-based CT. The evidence reviewed demonstrates that this treatment improves survival and reduces local recurrence rates compared to observation alone or RT alone after surgery.
- For patients receiving postoperative CRT, the optimal way of administering 5-fluorouracil (5FU) during CRT—via continuous infusion or bolus 5FU—is not clear, since neither method is definitively superior in terms of efficacy or toxicity (See Section 2. Part 2, Table 11 in the original guideline document for a description of differential toxicity patterns). Either method of administration can be considered appropriate, and treatments for individual patients should be based on an informed discussion of the potential risks and benefits of each mode of delivery.
- Informed discussions regarding the potential advantages of adjuvant therapy also need to address the significant acute and long-term toxicity that can potentially occur with combined treatment with RT and CT.
- It is the expert opinion of the Gastrointestinal Cancer Disease Site Group (GI DSG) that patients who have received preoperative CRT or RT should receive postoperative CT.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The recommendations are supported by systematic reviews, randomized controlled trials (RCTs), and meta-analyses.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Preoperative Therapy

- Two trials (2,3) comparing preoperative radiotherapy (RT) versus surgery alone for patients with resectable rectal cancer, including stage I to IV patients, presented outcomes separately for stage II and III patients. Subgroup analyses showed a significant local control benefit for preoperative RT in these patients. This is consistent with the local control benefit for all resectable rectal cancer patients reported in a Cochrane review (hazard ratio [HR], 0.71; 95% confidence interval [CI], 0.64-0.78; number needed to treat [NNT], 22; 95% CI, 17-29, assuming a control group local recurrence rate of 17% at five years).
- Two trials (5,6) comparing preoperative chemoradiotherapy (CRT) with standard fractionation longer course RT for patients with stage II and III rectal cancer found a local recurrence benefit and improved complete pathological response rate for patients who received CRT.

Postoperative Therapy

Twenty-nine RCTs, six meta-analyses on adjuvant RT and/or chemotherapy (CT) in stage II and III resected rectal cancer, and a review of the adverse effects of adjuvant RT and CT were reviewed. Some multi-arm trials contributed to more than one comparison. Data on overall survival and local failure were pooled for the following comparisons: RT versus observation alone, CT versus observation alone (systemic and oral), combined CRT versus observation, CT versus RT, CRT versus RT alone, and CRT versus CT alone (See Table 1 of the original guideline document).

Preoperative versus Postoperative Therapy

One trial comparing preoperative versus postoperative CRT (with 4 cycles of postoperative 5FU CT) for patients with clinical stage II and III rectal cancer showed superior local recurrence rate (relative risk [RR], 0.46; 95% CI, 0.26-0.82; from 6% to 13%) and lower acute and late toxicities in favour of preoperative CRT.

POTENTIAL HARMS

Not stated

CONTRAINDICATIONS

CONTRAINDICATIONS

For patients with relative contraindications to chemotherapy (CT) in the preoperative period, acceptable alternatives are preoperative standard fractionation (longer course; 45-50.4 gray [Gy] in 25-28 fractions) or hypofractionation (short course; 25Gy in 5 fractions) radiotherapy (RT) alone followed by surgery guided by the risk of adverse effects.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

- Recommendations for preoperative therapy presuppose adequate preoperative staging investigations, including transrectal ultrasound and/or magnetic resonance imaging (MRI) with surface or endorectal coil to assess the T category, MRI with surface or endorectal coil to assess the N category, a good digital rectal exam, computerized axial tomography (CAT) scan or MRI to assess the mesorectal margin, CAT scan or MRI of the abdomen to assess for potential metastatic or stage IV disease, and chest x-ray for pulmonary imaging.
- Potential inaccuracies of preoperative testing on tumour staging should be discussed with patients to allow them to make informed decisions.
- The eventual rectal surgery is expected to include total mesorectal excision (TME) principles. The quality of surgery greatly influences the potential benefits of preoperative treatments. A substantial number of trials included in the evidentiary base did not use currently recommended standards of surgery, including TME.
- In most instances, there should be a four to six-week delay from the completion of radiotherapy (RT) to surgery, to allow patients to recover to an optimal preoperative physiologic state. The exception is the use of short-course RT where, in relatively healthy patients, surgery can occur immediately following RT, and ideally within 10 days of the initiation of RT.
- Oxaliplatin-based chemotherapy (CT) and capecitabine have emerged as recommended treatments for the postoperative adjuvant therapy of high-risk colon cancer (see Program in Evidence-based Care [PEBC] Evidence-based Series Guideline #2-29). Patients with resected rectal cancer at similarly high risk of systemic recurrence should be offered the same systemic adjuvant therapy as their counterparts with resected colon cancer, based on the recommendations of Guideline #2-29. The rationale for this statement, in the absence of direct evidence for these agents in rectal cancer, is described in more detail in the Discussion section of the original guideline document for postoperative therapy (Section 2. Part 2).
- The rationale for the opinion that patients who have received standard fractionation (45-50.4 Gray [Gy] in 25-28 fractions) preoperative RT+/-CT should be offered postoperative CT in the absence of direct evidence for this is described in more detail in the Discussion section of the original guideline document for preoperative therapy (Section 2. Part 1).
- Enteritis, diarrhea, bowel obstruction or perforation, and fibrosis within the pelvis are associated with RT. Delayed adverse effects from RT include radiation enteritis (4%), small bowel obstruction (5%), rectal stricture (5%), pelvic fracture, and worsening sexual and bowel function. A greater number of hematological and non-hematological adverse effects are associated with CT plus RT than with CT alone or RT alone. Combined CT plus RT is associated

with acute gastrointestinal and hematologic adverse effects that may be severe or life threatening.
- Care has been taken in the preparation of the information contained in this report. Nonetheless, any person seeking to apply or consult the report is expected to use independent medical judgment in the context of individual clinical circumstances or seek out the supervision of a qualified clinician. Cancer Care Ontario makes no representation or guarantees of any kind whatsoever regarding the report content or use or application and disclaims any responsibility for its application or use in any way.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Getting Better
Living with Illness

IOM DOMAIN

Effectiveness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Wong R, Berry S, Spithoff K, Simunovic M, Chan K, Agboola O, Dingle B, Rumble RB, Cummings B, Gastrointestinal Cancer Disease Site Group. Preoperative or postoperative therapy for the management of patients with stage II or III rectal cancer: guideline recommendation. Toronto (ON): Cancer Care Ontario (CCO); 2008 Jul 15. 77 p. (Evidence-based series; no. 2-4). [72 references]

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

1998 Sep 5 (revised 2008 Jul 15)

GUIDELINE DEVELOPER(S)

Program in Evidence-based Care - State/Local Government Agency [Non-U.S.]

GUIDELINE DEVELOPER COMMENT

The Program in Evidence-based Care (PEBC) is a Province of Ontario initiative sponsored by Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

SOURCE(S) OF FUNDING

Cancer Care Ontario
Ontario Ministry of Health and Long-Term Care

GUIDELINE COMMITTEE

Gastrointestinal Cancer Disease Site Group

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

For a current list of members, please see the Cancer Care Ontario Web site.

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Members of the Gastrointestinal Cancer Disease Site Group (GI DSG) who were involved in the development of this systematic review and clinical practice guideline were polled for potential conflicts of interest and declared there were none.

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GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) from the Cancer Care Ontario Web site.

AVAILABILITY OF COMPANION DOCUMENTS

The following is available:

- Browman GP, Levine MN, Mohide EA, Hayward RSA, Pritchard KI, Gafni A, et al. The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. J Clin Oncol 1995;13(2):502-12.

PATIENT RESOURCES

Not available

NGC STATUS

This summary was completed by ECRI on August 19, 1999. The information was verified by the guideline developer as of September 17, 1999. This NGC summary was updated by ECRI on December 3, 2001. The updated information was reviewed by the guideline developer as of January 10, 2002. This summary was updated on July 30, 2003. The updated information was verified by the guideline developer on September 2, 2003. This summary was updated by ECRI Institute on December 16, 2008.

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